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SCIENCE MEDICINES HEALTH

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Committee on Herbal Medicinal Products (HMPC)

## Template for Assessment report for the development of European Union herbal monographs and European Union list entries

Final

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<sup>1</sup> Corrected reference to legislation: e.g. 'Directive 2001/83/EC as amended' replaced with 'Directive 2001/83/EC'

<sup>2</sup> Changes introduced in section 6 Overall conclusions



<date>  
<doc ref>

Committee on Herbal Medicinal Products (HMPC)

## Assessment report on <plant, plant part>

*Insert botanical name of the plant according to the binomial system (genus, species, variety and author), [comma] the plant part in Latin.*

<Draft><Final>

<Based on Article 10a of Directive 2001/83/EC (well-established use)>

<Based on Article 16d(1), Article 16f and Article 16h of Directive 2001/83/EC (traditional use)>

Herbal substance(s) (binomial scientific name of the plant, including plant part)	<Rapporteur to include text>
Herbal preparation(s)	<Rapporteur to include text>
Pharmaceutical form(s)	<Rapporteur to include text> <i>Pharmaceutical form only according to EDQM standard term.</i>
Rapporteur(s)	<Rapporteur to include text> <i>Name of HMPC/MLWP member (not Member State).</i>
Assessor(s)	<Rapporteur to include text>
Peer-reviewer	<Rapporteur to include text>

<Note: This draft assessment report is published to support the public consultation of the draft <European Union herbal monograph> <public statement> on <plant, plant part>. It is a working document, not yet edited, and shall be further developed after the release for consultation of the <monograph> <public statement>. Interested parties are welcome to submit comments to the HMPC secretariat, which will be taken into consideration but no 'overview of comments received during the public consultation' will be prepared on comments that will be received on this assessment report. The publication of this draft assessment report has been agreed to facilitate the understanding by Interested Parties of the assessment that has been carried out so far and led to the preparation of the draft <monograph> <public statement>.>

### *Note:*

- None of the main headings should be deleted during the preparation of the AR. Please insert 'not applicable'.*
- Table of contents should be updated regularly to maintain correct page numbering.*
- Any text should be written in the provided text boxes <Rapporteur to include text> only.*

- *All instruction notes (in green) must be deleted before finalising the AR.*
- *Remove footnotes where applicable.*
- *All tables to be numbered in sequential order.*

## Table of contents

<b>Table of contents</b> .....	<b>4</b>
<b>1. Introduction</b> .....	<b>6</b>
1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof ..	6
1.2. Search and assessment methodology .....	7
<b>2. Data on medicinal use</b> .....	<b>8</b>
2.1. Information about products on the market .....	8
2.1.1. Information about products on the market in the EU/EEA Member States .....	8
2.1.2. Information on products on the market outside the EU/EEA .....	9
2.2. Information on documented medicinal use and historical data from literature .....	9
2.3. Overall conclusions on medicinal use .....	10
<b>3. Non-Clinical Data</b> .....	<b>10</b>
3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof.....	11
3.1.1. Primary pharmacodynamics .....	11
3.1.2. Secondary pharmacodynamics .....	11
3.1.3. Safety pharmacology .....	12
3.1.4. Pharmacodynamic interactions .....	12
3.1.5. Conclusions .....	12
3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof.....	12
3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof .....	12
3.3.1. Single dose toxicity.....	12
3.3.2. Repeat dose toxicity.....	12
3.3.3. Genotoxicity .....	12
3.3.4. Carcinogenicity.....	12
3.3.5. Reproductive and developmental toxicity .....	13
3.3.6. Local tolerance .....	13
3.3.7. Other special studies.....	13
3.3.8. Conclusions .....	13
3.4. Overall conclusions on non-clinical data .....	13
<b>4. Clinical Data</b> .....	<b>13</b>
4.1. Clinical pharmacology .....	14
4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents.....	14
4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents.....	14
4.2. Clinical efficacy .....	14
4.2.1. Dose response studies.....	14
4.2.2. Clinical studies (case studies and clinical trials) .....	14
4.3. Clinical studies in special populations (e.g. elderly and children) .....	16
4.4. Overall conclusions on clinical pharmacology and efficacy.....	16
<b>5. Clinical Safety/Pharmacovigilance</b> .....	<b>16</b>
5.1. Overview of toxicological/safety data from clinical trials in humans.....	16

5.2. Patient exposure .....	18
5.3. Adverse events, serious adverse events and deaths.....	18
5.4. Laboratory findings.....	18
5.5. Safety in special populations and situations .....	19
5.5.1. Use in children and adolescents.....	19
5.5.2. Contraindications.....	19
5.5.3. Special Warnings and precautions for use .....	19
5.5.4. Drug interactions and other forms of interaction.....	19
5.5.5. Fertility, pregnancy and lactation.....	19
5.5.6. Overdose.....	19
5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability .....	19
5.5.8. Safety in other special situations .....	19
5.6. Overall conclusions on clinical safety.....	19
<b>6. Overall conclusions (benefit-risk assessment).....</b>	<b>20</b>
<b>&lt;Annex&gt; &lt;Annexes&gt; .....</b>	<b>22</b>

# 1. Introduction

## 1.1. Description of the herbal substance(s), herbal preparation(s) or combinations thereof

- Herbal substance(s)

<Rapporteur to include text>

*Insert reference to the relevant European Pharmacopoeia monograph or in absence thereof, to the monograph of a national pharmacopoeia or national codex currently used officially in a Member State. In their absence, reference to other bibliographic sources is possible. Rapporteur shall insert detailed specifications.*

- Herbal preparation(s)

<Rapporteur to include text>

*Insert reference to the relevant European Pharmacopoeia monograph or in absence thereof, to the monograph of a national pharmacopoeia or national codex currently used officially in a Member State. In their absence, reference to other bibliographic sources is possible. Rapporteur shall insert detailed specifications.*

*For above subsections:*

*According to the 'Procedure for the preparation of European Union monographs for traditional herbal medicinal products' (EMA/HMPC/182320/2005 Rev.2) and the 'Procedure for the preparation of European Union monographs for herbal medicinal products with well-established medicinal use (EMA/HMPC/182352/2005 Rev.2).*

*Includes a very short overview on main active compounds, common qualitative/quantitative characterisation, no detailed figures or structures.*

- Combinations of herbal substance(s) and/or herbal preparation(s) including a description of vitamin(s) and/or mineral(s) as ingredients of traditional combination herbal medicinal products assessed, where applicable.

<Rapporteur to include text or insert 'Not applicable'>

*According to the 'Guideline on the clinical assessment of fixed combinations of herbal substances/herbal preparations' (EMA/HMPC/166326/2005).*

## 1.2. Search and assessment methodology

<Rapporteur to include text>

*The Rapporteur shall undertake a comprehensive search on all available information and data which can be found in:*

*Books, Book chapters, articles and letters in Journals, Medical press reviews, Acts of law and regulations. Cross-reference to the list of references in Annex, which should list separately the references supporting the assessment report and the references used but which do not support the assessment report.*

*Additionally the Rapporteur shall use and list the online resources:*

- Scientific databases; medical databases (Medline, PubMed, Cochrane Database of Systematic Reviews, EMBASE, BioMed Central, PsycInfo, Micromedex,...); toxicological databases (TOXLINE)*
- Search engines used (Google, Google Scholar)*
- Other such as patients resources, social media resources*

*The Rapporteur should take into consideration information provided by the Member States relating to pharmacovigilance included in the market overview.*

*The Rapporteur shall also search for data, including alerts, from EU regulatory authorities (e.g. UKPAR) and non-EU regulatory authorities for examples Health Canada monographs or WHO monographs.*

*The Rapporteur shall describe the simple searches with key words.*

*The Rapporteur shall describe the advanced search methodology/strategy, key words, scheme, use of additional tools (MeSH).*

*Databases assessed (date, search terms) and other sources used.*

*If applicable (data availability), inclusion and exclusion criteria for literature, ideally differentiated between the main topics Non-clinical, Clinical, Safety.*

*Criteria for data inclusion and exclusion.*

*Software used for selection or processing data.*

<Books, Book chapters, articles and letters in Journals, Medical press reviews, Acts of law and regulations (cross-reference to the list of references in Annex).>

Search engines used: <Rapporteur to include text>

Scientific databases: <Rapporteur to include text>

Medical databases: <Rapporteur to include text>

Toxicological databases: <Rapporteur to include text>

Pharmacovigilance resources: <Rapporteur to include text>

Data from EU and non-EU regulatory authorities: <Rapporteur to include text>

Other resources: <Rapporteur to include text>

## 2. Data on medicinal use

### 2.1. Information about products on the market

#### 2.1.1. Information about products on the market in the EU/EEA Member States

*According to the information provided by the National Competent Authorities. Data are collected using the template entitled 'Document for information exchange for the preparation of the assessment report for the development of European Union monographs and for inclusion of herbal substance(s), preparation(s) or combinations thereof in the list' (EMA/HMPC/137093/2006).*

*The information on the regulatory status of the products may preferably include the nature of the authorisation granted for the product to access the market (MA based on full or mixed application, MA based on bibliographic application as per Article 10a of Directive 2001/83/EC, traditional use registration, etc.) to establish the period of medicinal use:*

- for TU: at least 30 years of medicinal use including at least 15 years in the EU*
- for WEU: at least 10 years of MA in the EU.*

#### Information on medicinal products marketed in the EU/EEA

Table <insert number>: Overview of data obtained from marketed medicinal products

<b>Active substance</b>	<b>Indication</b>	<b>Pharmaceutical form</b> <i>Strength (where relevant)</i> <i>Posology</i> <i>Duration of use</i>	<b>Regulatory Status</b> <i>(date, Member State)</i>
<i>To be given according to the declaration guideline</i>	<i>As reported in the market overview</i>	<i>Only restriction to duration of use may be reported</i>	<i>Brand names can be kept during discussion and shall be deleted at publication stage</i>

This overview is not exhaustive. It is provided for information only and reflects the situation at the time when it was established.



### **Information on relevant combination medicinal products marketed in the EU/EEA**

<Rapporteur to include text or insert 'Not applicable'>

*Include any other information on combination medicinal products considered relevant for the establishment of the monograph.*

<insert Member State name>

<insert text Product name>

<insert Pharmaceutical form> containing <insert text>

Indication: <insert text>

Posology: <insert text>

On the market since <insert date>.

### **Information on other products marketed in the EU/EEA (where relevant)**

<Rapporteur to include text or insert 'Not applicable'>

*Include any other relevant information on products available on the market which are neither authorised nor registered (e.g. medical devices, food/dietary supplements, cosmetics).*

*The information can be provided using the same format (table) as for the information on medicinal products.*

### **2.1.2. Information on products on the market outside the EU/EEA**

<Rapporteur to include text or insert 'Not applicable'>

*Include information on products marketed outside the EU/EEA if available (data from literature to be reported only in section 2.2).*

*The information can be provided using the same format (table) as for the information on medicinal products marketed in the EU.*

### **2.2. Information on documented medicinal use and historical data from literature**

<Rapporteur to include text>

*For each herbal preparation, provide evidence of history and extent of use, obtained from literature, and preferably classified whether predominantly European or non-European tradition, and the current use.*

*For each herbal preparation, provide information on traditional/current indication(s), specified strength and posology, route of administration, duration of use per indication. Evaluation on the use should be presented both on the known use(s) in the EU, and, if applicable, use(s) outside the EU.*

Table <insert number>: Overview of historical data

Herbal preparation	Documented use / Traditional use	Pharmaceutical form <i>Strength (where relevant)</i> <i>Posology</i> <i>Duration of use</i>	Reference

### 2.3. Overall conclusions on medicinal use

<Rapporteur to include text>

*For each herbal preparation accepted in the monograph, provide an overview of the available sources (market data and/or literature) that provide evidence of:*

- period of use*
- specified strength and specified posology*
- indications suitable to the legal requirements in the relevant route of administration. The Rapporteur should discuss all available sources showing that the requirements for the period of medicinal use are fulfilled:*
  - for TU: at least 30 years of medicinal use including at least 15 years in the EU*
  - for WEU: at least 10 years of MA in the EU.*

Table <insert number>: Overview of evidence on period of medicinal use

Herbal preparation Pharmaceutical form	Indication	Posology, Strength	Period of medicinal use

## 3. Non-Clinical Data

<Rapporteur to include text>

*For all studies cited, it should be stated by means of a detailed description which herbal substance(s)/herbal preparation(s) have been used and information should be provided for each preparation separately (if such information are not known from the reference, this should be stated as well). The studies should be organised in studies performed with preparations covered by the monograph (or similar preparations), other preparations (different to those covered by the monograph) and single (isolated) substances).*

*For all studies cited, it should be stated clearly, which concentrations/dosage have been used and in which concentrations/*

*dosages effects were seen; it should be stated if e.g. a IC<sub>50</sub> or EC<sub>50</sub> was calculated.*

*The Rapporteur should discuss the relevance of the findings in relation to the herbal preparations accepted in the monograph. A comparison to the attended dosage in humans (for in-vivo-data) keeping in mind the re-calculation to the HED) should be given. For in-vitro data it should keep in mind that for clear effects seen in concentrations of >100 µg/ml a physiological correlation is not plausible.*

*All the studies should be assessed and a clear statement should be given, if the results are sufficient to support the usage in the indication of the monograph or not.*

*If no information is available or necessary under a specific heading, that section should be marked "no data found/available" or "not relevant".*

### **3.1. Overview of available pharmacological data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof**

#### **3.1.1. Primary pharmacodynamics**

<Rapporteur to include text>

*The Rapporteur shall describe the pharmacological data in connection to the indication(s) agreed in the monograph.*

Table <insert number>: Overview of the main non-clinical data/conclusions

<b>Herbal preparation tested</b>	<b>Posology</b> <i>Strength</i> <i>Dosage</i> <i>Route of administration</i>	<b>Experimental model</b> <i>In vivo/</i> <i>In vitro</i>	<b>Reference</b> <i>Year of publication</i>	<b>Main non-clinical conclusions</b>
comparable/similar preparations to preparations of the monograph				
other preparations				
single substances				

#### **3.1.2. Secondary pharmacodynamics**

<Rapporteur to include text>

*The Rapporteur shall briefly describe the results from studies which are not connected to the indication(s) agreed in the monograph.*

### **3.1.3. Safety pharmacology**

<Rapporteur to include text>

### **3.1.4. Pharmacodynamic interactions**

<Rapporteur to include text>

### **3.1.5. Conclusions**

<Rapporteur to include text>

*The conclusions shall include statements on the presence and usefulness of the data.*

*The Rapporteur should discuss the relevance of the findings in relation to the herbal preparations accepted in the monograph, especially as regards to the posology used in the animal testing in comparison to the therapeutic posology in humans.*

## **3.2. Overview of available pharmacokinetic data regarding the herbal substance(s), herbal preparation(s) and relevant constituents thereof**

<Rapporteur to include text>

*If possible the Rapporteur to differentiate between Absorption, Distribution, Metabolism, Elimination and Pharmacokinetic interactions with other medicinal products.*

*The Rapporteur shall include statements on the presence and usefulness of the data.*

## **3.3. Overview of available toxicological data regarding the herbal substance(s)/herbal preparation(s) and constituents thereof**

<Rapporteur to include text>

### **3.3.1. Single dose toxicity**

<Rapporteur to include text>

### **3.3.2. Repeat dose toxicity**

<Rapporteur to include text>

### **3.3.3. Genotoxicity**

<Rapporteur to include text>

### **3.3.4. Carcinogenicity**

<Rapporteur to include text>

### **3.3.5. Reproductive and developmental toxicity**

<Rapporteur to include text>

### **3.3.6. Local tolerance**

<Rapporteur to include text>

### **3.3.7. Other special studies**

<Rapporteur to include text>

### **3.3.8. Conclusions**

<Rapporteur to include text>

*The Rapporteur shall include statements on the presence and usefulness of the data.*

*The Rapporteur shall discuss adverse reactions, potential or manifest, of constituents with safety concerns (e.g. estragole, thujone etc).*

## **3.4. Overall conclusions on non-clinical data**

<Rapporteur to include text>

*Includes evidence/plausibility discussion by relation of available data to the indications and herbal preparations specified in section 2.3.*

*The Rapporteur may consider the possible inclusion of examples provided below.*

<Non-clinical data on <insert> activity supports the traditional use as <insert>.>

<Results from relevant experimental studies on <insert> to support the proposed indications are very limited. The reported pharmacological effects are not considered contradictory to the traditional uses.>

<Specific data on pharmacokinetics and interactions are not available.>

<Non-clinical information on the safety of <insert> is scarce.>

<As there is no information on reproductive and developmental toxicity, the use during pregnancy and lactation cannot be recommended.>

<Oral><and><cutaneous><insert other> administration of <insert> can be regarded as safe at <traditionally> used doses with the exception of patients with severe renal or cardiac disease e.g. renal and heart failure.>

<Tests on reproductive toxicity, genotoxicity and carcinogenicity have not been performed. >

## **4. Clinical Data**

*For all studies cited, it should be stated by means of a detailed description which herbal substance(s)/herbal preparation(s) have been used and information should be provided for each preparation separately.*

## **4.1. Clinical pharmacology**

### **4.1.1. Overview of pharmacodynamic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents**

<Rapporteur to include text>

### **4.1.2. Overview of pharmacokinetic data regarding the herbal substance(s)/preparation(s) including data on relevant constituents**

<Rapporteur to include text>

## **4.2. Clinical efficacy**

<Rapporteur to include text>

### **4.2.1. Dose response studies**

<Rapporteur to include text>

### **4.2.2. Clinical studies (case studies and clinical trials)**

<Rapporteur to include text>

*For each therapeutic area, a separate table should be inserted.*

*Information on undesirable effects is to be addressed under section 5 'Clinical Safety'*

Table <insert number>: Clinical studies on humans, in <insert therapeutic area>

Type (aim) and objective(s) of Study Reference	Study Design and Type of Control Study duration (if available)	Test Product(s) herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment	Number of subjects (including age, sex, drop out)	Healthy Type of subjects or Diagnosis of Patients (inclusion criteria)	Outcomes (primary and secondary endpoints)	Statistical analysis (e.g. ITT yes/no, CI 95%) Quality score e.g. Jadad score	Comments on Clinical relevance of results

### **4.3. Clinical studies in special populations (e.g. elderly and children)**

<Rapporteur to include text>

### **4.4. Overall conclusions on clinical pharmacology and efficacy**

<Rapporteur to include text>

*The conclusions should include an assessment of the plausibility of efficacy of the herbal preparation(s)/medicinal product on the basis of long-standing use and experience.*

## **5. Clinical Safety/Pharmacovigilance**

### **5.1. Overview of toxicological/safety data from clinical trials in humans**

<Rapporteur to include text>

*For each therapeutic area, a separate table should be inserted.*



Table <insert number>: Clinical safety data from clinical trials

<b>Type (aim) and objective (s) of Study Reference</b>	<b>Study Design and Type of Control Study duration (if available )</b>	<b>Test Product(s) herbal preparation, pharmaceutical form; Dosage Regimen; Route of Administration Duration of treatment</b>	<b>Number of subjects (including age, sex, drop out)</b>	<b>Healthy Type of subjects or Diagnosis of Patients (inclusion criteria)</b>	<b>Adverse reactions</b>	<b>Comments on clinical relevance of results</b>

## **5.2. Patient exposure**

<Rapporteur to include text>

*Information on patient exposure coming from:*

- *pre-marketing (number of patients in clinical trials)*
- *post-marketing (information from PSUR).*

*NB: The Rapporteur may comment on information derived from MA based on WEU provisions for which a quantitative judgement of the use of the substance is undertaken.*

*Information on the exposure related to uses under other regulatory frameworks (food/cosmetics/other products).*

*The Rapporteur may consider the possible inclusion of the following examples.*

<No data available.>

<Aside from market presence and data from studies, there are no concrete data concerning patient exposure.>

<Data obtained from <insert number> patients, tested for safety during clinical trials, showed the following results:>

<Rapporteur to include text>

*Rapporteur to specify the frequency of adverse reactions.*

<If patients with known intolerance to <insert>, or plants of the <insert> family are excluded, a traditional use is possible if administration follows the instructions as specified in the monograph.>

<Rapporteur to include text>

## **5.3. Adverse events, serious adverse events and deaths**

<Rapporteur to include text>

*To avoid repetition, the Rapporteur shall consider making cross-reference to section 5.2.*

## **5.4. Laboratory findings**

<Rapporteur to include text>

*Information on laboratory findings (results of laboratory testing in blood, urine, etc., changes of blood pressure or heart rate or ECG parameters) coming from:*

- *pre-marketing (results of laboratory testing and changes of other parameters examined in clinical trials)*
- *post-marketing (information from PSUR).*

*The Rapporteur may consider the possible inclusion of the following examples.*

<No data available.>

<The value of <insert parameter> did not change during an <insert number>-month long study (<insert reference to publication>).>

## **5.5. Safety in special populations and situations**

<Rapporteur to include text>

### **5.5.1. Use in children and adolescents**

<Rapporteur to include text>

### **5.5.2. Contraindications**

<Rapporteur to include text>

### **5.5.3. Special warnings and precautions for use**

<Rapporteur to include text>

### **5.5.4. Drug interactions and other forms of interaction**

<Rapporteur to include text>

### **5.5.5. Fertility, pregnancy and lactation**

<Rapporteur to include text>

### **5.5.6. Overdose**

<Rapporteur to include text>

### **5.5.7. Effects on ability to drive or operate machinery or impairment of mental ability**

<Rapporteur to include text>

### **5.5.8. Safety in other special situations**

<Rapporteur to include text or insert 'Not applicable'>

*The Rapporteur shall include, when available, data and information on intrinsic factors (e.g. patients' characteristics such as gender, race, polymorphic metabolism)/Extrinsic factors, Drug abuse, Withdrawal and rebound.*

## **5.6. Overall conclusions on clinical safety**

<Rapporteur to include text>

*Includes a discussion on the evidence that the medicinal product, on the basis of the information on its traditional use, proves not to be harmful in the specified conditions of use (recommended indications/recommended preparations).*

## 6. Overall conclusions (benefit-risk assessment)

<Rapporteur to include text>

*This section should cover all recommended 'well-established use' and 'traditional use' indications.*

*A conclusion shall be provided for each therapeutic indication and each herbal preparation. The choice for the wording of traditional use indications vis-à-vis existing wordings in monographs in the same therapeutic area should be briefly discussed/justified.*

*The clinical studies supporting well-established use should be specified for each therapeutic indication and each herbal preparation.*

*If well-established use was not accepted, the reasons should be stated.*

*The conclusion should justify whether*

*- all the requirements for WEU (period of medicinal use, acceptable level of safety, recognised efficacy, quantitative aspects of the use of the substance and the degree of scientific interest in its use) are met*

*- all the requirements for TU (self-medication character, specified strength/posology, appropriate route of administration, period of traditional use, plausibility and safety) are met. A clear statement for the justification of the plausibility of traditional use must be added.*

*Benefit-risk balance should be addressed in this section and the available data both favourable and unfavourable should be evaluated. A specific conclusion should be presented on the benefit-risk balance in the specified conditions of use, including special warnings and/or contraindications. Statement on the outcome of the benefit-risk assessment on the presence of constituents with safety concerns (such as estragole or anethole) should be given. Reference can be made to the document 'Check-list for the benefit-risk assessment' (EMA/HMPC/562654/2008).*

*Insert the chosen proposed ATC code for each WEU indication and the therapeutic area for browse search for each TU indication.*

*Rapporteur to provide information on the presence and identity of a (group of) constituent(s) with known therapeutic activity<sup>3</sup> or an (group of) active marker(s)<sup>4</sup> in the herbal substance/herbal preparation in order to allow a possible classification of the herbal substance/preparation according to the definitions given in the Guideline on quality of herbal medicinal products/traditional herbal medicinal products (CPMP/QWP/2819/00 as revised) and in the Ph. Eur. monograph on extracts. Where possible typical analytical marker(s)<sup>3</sup> should be indicated*

*The Rapporteur may consider the possible inclusion of the following examples.*

<No constituent with known therapeutic activity or active marker can be recognised by the HMPC>

<Typical analytical marker(s) <is><are> <insert name of the constituent/s>

< <On the basis of the available information <insert name of the constituent/s> <is><are> considered by the HMPC as contributing to the activity of the <insert name of herbal substance/herbal preparation(s)> and therefore <it> <they> might be used as <an> <active marker<s>> (for quantified herbal substances/preparations).>

< <insert name of the constituent/s> <is><are> considered by the HMPC as <an> <constituent<s> with known therapeutic activity> >. (expected only for standardized herbal substances/preparations).>

*The conclusions should include a statement pointing to the possibility/non-possibility to support a European Union list entry.*

*The Rapporteur may consider the possible inclusion of the following examples when a list entry is supported.*

<The data on safety are considered sufficient to support a European Union list entry for the <above mentioned> <following> herbal preparations and indications.>

<Where relevant Rapporteur to include text>

<A European Union list entry for <insert text> is supported only for <adolescents over 12 years,><adults and elderly>, considering the small amount of <insert name of constituent(s)/HP with safety concerns> in <insert HP> prepared from <insert HS>.>

<A European Union list entry for <insert text> is supported only in <insert indication>, considering the <small><negligible> amount of <insert name of constituent(s)/HP with safety concerns><compared to the background exposure due to <food intake> <or> <and> <cosmetic use>> when <administered><taken>< used> at the specified posology.>

---

<sup>3</sup> **Constituents with known therapeutic activity:** are chemically defined substances or groups of substances, which are generally accepted to contribute substantially to the therapeutic activity of a herbal substance, a herbal preparation or a herbal medicinal product.

<sup>4</sup> **Markers:** are chemically defined constituents or groups of constituents of a herbal substance, a herbal preparation or a herbal medicinal product which are of interest for control purposes independent of whether they have any therapeutic. Markers serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the herbal medicinal product if the marker has been quantitatively determined in the herbal substance or herbal preparation.

There are two categories of markers:

**Active markers** are constituents or groups of constituents which are generally accepted to contribute to the therapeutic activity.

**Analytical markers** are constituents or groups of constituents that serve for analytical purposes.

*The Rapporteur may consider the possible inclusion of the following examples when a list entry is not supported.*

<A European Union list entry is not supported due to lack of <adequate> data on genotoxicity.>

<Tests on genotoxicity have been performed <with <insert HS/HP>> <and><or><with the isolated <substance><substances> <insert name(s)>> only; these data cannot be extrapolated to <insert HS/HP>. Therefore a European Union list entry cannot be supported due to lack of adequate data.>

## **<Annex> <Annexes>**

### ***List of references***

*All references supporting the assessment report should be attached as a separate document (using appropriate template) and, if applicable, including in a separate section the references which were read but do not support the assessment report.*